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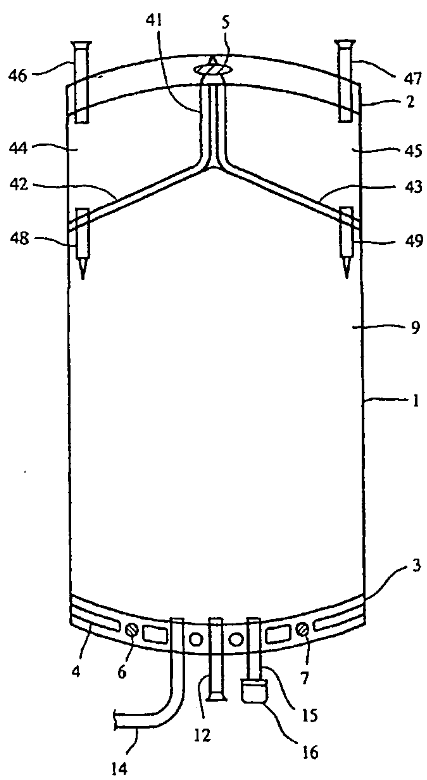

(57) Abstract: The invention relates to a multiple compartment container for sterile medical solutions, particularly solutions for peritoneal dialysis containing a carbohydrate stabilisation compound, a carbohydrate medical solution containing said carbohydrate stabilisation compound and a method for the preparation thereof.

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CARBOHYDRATE MEDICAL SOLUTION AND SULPHITE STABILISATOR IN A MULTIPLE COMPARTMENT CONTAINER AND USE THEREOF

TECHNICAL FIELD

The present invention relates to multiple compartment containers including sterile medical solutions, in which at least one solution contains carbohydrate compounds. The invention further relates to stabilising carbohydrates in a sterile medical solution.

BACKGROUND

Sterilisation of medical solutions such as, for example, peritoneal dialyses (PD) solutions, is commonly performed through the addition of energy, either in the form of radiation or heat. WO-A-9705852 discloses a multiple compartment container including sterile peritoneal dialyses solutions, which is heat-sterilised in an autoclave.

In recent years scientists have become aware of the toxicity of decomposition compounds of carbohydrates in PD solutions. Wieslander et al., reported that all major brands of commercial PD solutions were toxic in contrast to PD solutions sterilised by filtration (Wieslander et al., 1991, Kidney Int, 40:77-79). The PD solutions were tested after dilution with cell growth media on cultured fibroblasts. Furthermore, Wieslander et al. have reported that the glucose degradation products also affect the functional responses involved in host defence (Wieslander et al., 1995, Peritoneal Dialysis Int, 15 (suppl).

A patient on peritoneal dialysis (PD) uses between 8 and 20 litres of dialysis solution every day, depending on the treatment. This results in the consumption of 3-7 tons of solution with 1.5-4% glucose (50-175 kg pure glucose) every year. (Wieslander, 1996, Nephrol Dial Transplant 11:958-959), which if the glucose undergoes decomposition also means a non-negligible amount of decomposition compounds. Furthermore, it is well known that some patients experience pain during inflow of the dialysis fluid. It has been speculated that the pain could be the result of glucose degradation (Henderson et al., 1985 Frontiers in peritoneal dialysis, ed.

Winchester, New York: Field, Rich, 261-264) and that these degradation products mediate basal cytotoxicity (Barile FA, 1994, Introduction to *in vitro* cytotoxicity. Florida:CRC Press, 27-35). This means that they act upon fundamental life processes, which involve structures and functions common to all living cells such as membrane integrity, mitochondrial activity, or synthesis of proteins and DNA. These basal cell functions support organ specific cell functions. Thus, glucose degradation products capable of affecting basal cell activities are likely to interfere with specialised cell functions such as IL-1β release from mononuclear cells.

Glucose, an osmotic agent commonly used in PD solutions is known to degrade into carbonyls such as formaldehyde, acetaldehyde, metylglyoxal, 3-deoxyglucosone and glyoxal.

Sulphite compounds have commonly been used as antioxidant in parenteral emergency drugs to prevent oxidation. The mechanism of decomposition of carbohydrates in PD solutions has appears however to have less to do with oxidation and sulphite is not intended to be used as an antioxidant *in vitro* in the present invention. Further, the anti-microbial or antioxidant compounds in parenteral emergency drugs are typically used in concentration which deliver 0.5 to 2 mg of sulphite per ml of undiluted drug injection (Smolinske S, 1992, Clinical toxicology 30:597-606). Such concentrations for preventing oxidation could not be used in PD solutions since they would administer too much sulphite to the patient resulting in adverse toxic effects.

SUMMARY OF THE INVENTION

On the above background it is an object of the present invention to provide a multiple compartment container for sterile medical solutions of the kind referred to above in which decomposition of carbohydrates and/or the negative effects of the decomposition products are reduced. The multiple compartment container comprises at least one sulphite compound in one or more of the compartments to stabilise decomposition of carbohydrates or to scavenge decomposition products formed during sterilisation and/or storage.

The invention further relates to a medical solution wherein the solution contains at least one carbohydrate compound and at least one sulphite compound to stabilise decomposition of the carbohydrates or to scavenge decomposition products formed from the carbohydrates during sterilisation or storage of the medical solutions.

Additionally the invention relates to a method of stabilising a carbohydrate containing solution wherein the solution contains at least one sulphite compound to stabilise decomposition of carbohydrates or to scavenge decomposition products formed during sterilisation and/or storage.

Furthermore the invention relates to the use of a carbohydrate containing solution for the preparation of a multiple compartment container.

Finally, the invention relates to use of a carbohydrate containing solution for the preparation of a multiple compartment container for the treatment of a patient in need thereof.

BRIEF DESCRIPTION OF THE DRAWING

In the following detailed portion of the present description, the invention will be explained in more detail with reference to an exemplary embodiment shown in the drawings, in which Figure 1 is a frontal view on a multiple compartment container according to an embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention is intended for use in treatments of diseases such as uremic disorder or kidney malfunctions, including for example treatments of diseases using peritoneal dialysis.

Definitions

The term "multiple compartment container for a medical solution" is intended to mean any container comprising more than one compartment, particularly two or three but not limited to three, compartments. One example is a multiple compartment container used for peritoneal dialysis containing medical solutions, which are sold under the brand Physioneal® and Gambrosol® trio.

The term "medical solution" is intended to mean any solution useful for medicinal purposes in which, a carbohydrate may be present and in which the carbohydrate undergoes decomposition during either the sterilisation procedure or storage resulting in disadvantageous decomposition products unfavourable for living cells. Decomposition products contemplated are for example products such as mono and dicarbonyl compounds, formaldehyde, acetaldehyde, methylglyoxal, 3-deoxyglucosone and glyoxal or the like. The storage conditions could be any conventional storage condition, such as room temperature for 2 years. One example of a medical solution is a solution, present in one or more of the compartments, used for peritoneal dialysis.

The term "final solution" is intended to mean a solution obtained by mixing one or more of the medical solutions in the container.

The term "peritoneal dialysis solution" is intended to mean a solution comprising an electrolyte, a buffer and an osmotically active compound, wherein the electrolyte comprises ions, such as sodium, potassium, calcium and magnesium; the buffer comprises components, such as acetate, lactate and bicarbonate; and the osmotic compound is a carbohydrate as defined hereinafter. Examples of medical solutions for use as peritoneal dialysis solutions may be found in Wieslander et al., 1991, Kidney Int 40:77-79. The peritoneal dialysis solution could, prior to dialysis, be present in one or more compartments. In the case of multiple compartments the solutions are mixed prior to peritoneal dialysis.

The term "carbohydrate compound" is intended to mean sugars or sugars acids such as glucose, fructose, mannose, aldonic, alduronic, aldaric acids and their esters with saccharides or a polymer of glucose, fructose, mannose, aldonic, alduronic, aldaric acids and their esters with saccharides or a synthetic form of

glucose, fructose, mannose, aldonic, alduronic, aldaric acids and their esters with saccharides or derivatives and mixtures thereof.

The term "sulphite compound" is intended to mean a sulphite containing compound with the properties to reduce the content of decomposition products, by for example stabilising the solution, including preventing the generation of decomposition products, or scavenging already formed decomposition products, produced during sterilisation and/or storage of medical solutions containing carbohydrate compounds, as defined above.

Furthermore, the sulphite compound could be used as an antioxidant or to scavenge toxic or allergenic compounds *in vivo*, such as in the body fluids. Examples of such toxic or allergenic compounds are metylglyoxal, 3-deoxyglucosone and glyoxal. The effect of the sulphite compound can be measured according to the method "*Analysis of glucose degradation products*" mentioned under "Material and Methods" hereinafter. Examples of such sulphite compounds are any sulphite, having a positive counter ion, such as sodium, potassium, calcium, magnesium and ammonium, for example HSO_3^-, $S_2O_5^{2-}$ and SO_3^{2-}. Examples of sulphite compounds to be used are $NaHSO_3$, $Na_2S_2O_5$ and Na_2SO_3 or any other of sulphite compound or derivative thereof, natural or synthetic, or mixtures thereof.

The term "stabilising" is intended to mean preventing the generation of decomposition products, or scavenging already formed decomposition products, produced during sterilisation and/or storage of medical solutions containing carbohydrate compounds

The term "carbohydrate decomposition products" is intended to mean products produced in a carbohydrate solution during any kind of sterilisation and/or during storage, which are products obtained from decomposition of carbohydrates, such as glucose and toxic to eucaryotic and procaryotic cells. Specifically contemplated are mono and dicarbonyl compounds, such as formaldehyde, acetaldehyde, methylglyoxal, 3-deoxyglucosone and glyoxal or the like. The toxicity can be measured according to the method "*in vitro* assay for cytotoxity" mentioned in "Materials and Methods hereinafter.

The term “sterilisation” is intended to mean any kind of sterilisation, such as radiation, pressure, heat, UV-radiation, radioactive radiation, sterile filtration, radiation using micro waves or other sterilisation methods. Furthermore the sterilisation can be performed using different approaches such as short sterilisation time at a high temperature, sterilisation at low pH, sterilisation with high glucose concentration after removal of catalytic substances.

Multiple compartment containers employing a medical solution.

The invention relates to multiple compartment containers for sterile medical solutions, particularly solutions for peritoneal dialysis (PD), wherein the medical solutions are present in one or more compartments. One or more of the compartments comprises a carbohydrate and at least one sulphite compound in order to reduce the amount of the carbohydrate decomposition products produced during sterilisation and/or storage. Furthermore one or more of the compartments may include an electrolyte, a buffer and any other pharmaceutically acceptable additive or other component.

Additionally, the container comprises at least two compartments, preferably three or more compartments, most preferably three. In at least one of the compartments there is provided a carbohydrate compound in solution and in at least one of the compartments there is provided a sulphite compound to reduce the formation or scavenge already produced decomposition products formed from carbohydrate. Furthermore the "sulphite compound" could be used as an antioxidant or to scavenge toxic or allergenic compounds *in vivo*, such as in the body fluids. Commonly used medical solutions either in single or multiple compartment container(s) for peritoneal dialysis preferably contain glucose in the final solution in a concentration in the range of 1.5 to 4,0 % preferably substantially 1.5, 2.5 or 4 % by weight (based on the final solution).

Fig. 1 shows a preferred embodiment of the container, in this case a three-compartment bag . The bag 1 is made from a continuous tube of a plastics material, which is sealed at both ends by sealing borders 2,3.

As shown in FIG. 1 each sealing border comprises several embossments 4 and apertures 5,6,7. The embossments 4 enhance the stability of the border 2. The aperture 5 in the upper border 2 is intended for hanging the bag during use and the apertures 6,7 in the lower border 3 are for fixation of the bag during the manufacturing operation.

The lower border 3 is also provided with an outlet tube 14, which connects compartment 9 with the consumer, for example a catheter ending in the abdominal cavity of a patient for peritoneal dialysis. Often tube 14 terminates in a luer connector (not shown in FIG. 1).
Furthermore, border 3 is provided with a filling tube 12, a medicament tube 15 including a removable cap 16. When cap 16 is removed, tube 15 forms an entrance site for introducing any type of beneficial agent or medicament into compartment 9 as desired, such as antibiotics.

The bag 1 is divided into three compartments 9,44,45 by welding seal lines 41,42,43. The upper compartments 44,45 divided by welding seal line 11 are of equal size and separated form the lower compartment 8 by two sloping welding lines 42,43. Thus there is formed a first upper compartment 44 and a second upper compartment 45, each being accessed via introduction tubes 46,47. The large lower compartment 9 comprises the electrolytes necessary for the solution to be formed (final solution), such as NaCl, $MgCl_2$, lactate etc., dissolved in water in a manner known per se.

The first compartment 44 comprises glucose solution having a concentration of about 30% and the second compartment 45 comprises a glucose solution having a concentration of about 50%.

When breaking the breakable portion of connection tube 48, the contents of the first compartment 44 is mixed with the contents of the lower compartment 9 to form a peritoneal dialysis solution having a concentration of 1.5% of glucose. If the breakable portion of connection tube 49 is broken, the contents of compartment 45

is mixed with the contents of both compartment 9 thereby forming a dialysis solution having a concentration of about 2.5% of glucose. If both breakable portions of connection tubes 48,49 are broken, the contents of both compartments 44 and 45 are mixed with the contents of compartment 9 thereby to form a dialysis solution having a concentration of about 4% of glucose. The above dialysis solutions formed by mixing at least one of the glucose containing compartments.

If the bag should be used as a nutritional solution, the large compartment 9 may comprise only NaCl or any other suitable composition as used today but excluding glucose.

It is mentioned that the glucose can be exchanged with a glucose like component, such as glucose polymers, as an osmotic agent.

Furthermore, the sterile medical solutions comprising a carbohydrate, may include an electrolyte, a buffer such as lactate and any other pharmaceutically acceptable additive.

According to one embodiment of the invention the carbohydrate compound is separately provided in one or more compartments, the rest of the peritoneal dialysis solution compounds being provided in one or more the other compartments. The sulphite compound(s) may be present in one or more of said compartments or separately presented in one or more compartments. The sulphite compound(s) may be introduced in any of the carbohydrate or electrolyte solution compartments before or after sterilisation. However, some or all components of the medical solution(s) and the sulphite compound are mixed prior to peritoneal dialysis to obtain a final solution.

If a monosulphite compound such a bisulphate is used, it is preferably added to the carbohydrate and/or the electrolyte compartment in an amount to give a final solution within the range of 0.01 - 10 mM, preferably 0.05 - 1 mM, most preferably 0.05 - 0.5 mM. If a disulphite compound is used it is preferably added to the carbohydrate compartment in an amount to give a final solution within the range of 0.005 - 5 mM, preferably 0.025 - 0.5 mM, most preferably about 0.025 – 0.25 mM.

If a disulphite compound is used it is preferably added in an amount to give a final solution which is half of the concentration used for the corresponding monosulphite compound.

The pH of the solution in the carbohydrate compartment is preferably between pH 2.0-7.5, more preferably pH 2-5.5, even more preferably pH 3-4 and most preferably about pH 3.2. The pH of the final solution is preferably between 5.0 – 8.0, more preferably between 6.5 – 8.0, most preferably between 7.0 – 7.5 or absolutely most preferably 7.4.

Additionally, in a preferred embodiment, the multiple compartment container containing the medical solution is sterilised. Any conventional methods and apparatus for sterilisation may be used, such as those mentioned under the definition of the term "sterilisation". Preferably the sterilisation is performed by heat treatment most preferable at about 121° C for 20 minutes (Ph. Eur. (current)).

Solution

The invention further relates to a medical solution comprising at least one sulphite compound to be included for the ability to reduce the concentration of decomposition products formed from a carbohydrate by stabilisation or scavenging already formed decomposition products, obtained during sterilisation and/or storage of solutions containing carbohydrate compounds, as defined above. Furthermore the "sulphite compound" could be used as an antioxidant or to scavenge toxic or allergenic compounds *in vivo*, such as in the body fluids.

The invention further relates to a medical solution such as a solution used for peritoneal dialysis either in a single or a multiple compartment container, comprising at least one sulphite compound to be included for the ability to reduce decomposition of a carbohydrate present in the solution exposed to sterilisation.

If a monosulphite compound such a bisulphite is used, it is preferably added to the carbohydrate and/or the electrolyte compartment in an amount to give a final solution with a concentration within the range of 0.01 - 10 mM, preferably 0.05 - 1 mM, most preferably about 0.05 – 0.5 mM. If a disulphite compound is used it is

preferably added to the carbohydrate compartment in an amount to give a final solution with a concentration within the range of 0.005 - 5 mM, preferably 0.025 - 0.5 mM, most preferably 0.025 - 0.25 mM.

If a disulphite compound is used it is preferably added in an amount to give a final solution which is half of the concentration used for the corresponding monosulphite compound.

The pH of the carbohydrate solution is not critical and could be in any range, suitable the pH is between pH 2.0-7.5, more preferably pH 2-5.5, even more preferably pH 3-4 and even more preferably about pH 3.2. The pH of the final solution is preferably between 5.0 – 8.0 and more preferably 6.5 – 8.0 and most preferably 7.0 – 7.5.

Preferably the medical solution is a sterile medical solution.

Additionally, the sulphite compound may be provided to the carbohydrate solution prior or after sterilisation.

Furthermore, the sterilisation is performed using any conventional sterilisation method as defined above under the term "sterilisation". Preferably the sterilisation is performed by heat treatment within the range of 100-150° C, for 1-130 minutes, more preferably at 121° C for 20 minutes (Ph. Eur. (current)).

The solution may be any medical solution which comprises a carbohydrate with or without other components. Preferably the solution is a medical solution such as a solution used for peritoneal dialysis, preferably medical solution(s) for single or multiple compartment container(s) for peritoneal dialysis, more preferably two or three compartment containers, even more preferably a three compartment container. Medical solutions used for peritoneal dialysis preferably contain glucose in an amount to give a glucose concentration in the range of 1.5 to 4%, preferably about 1.5, 2.5 or 4 % by weight in the final solution (based on the total final solution).

Additionally the medical solution is a solution used to scavenge toxic or allergenic compounds *in vivo*, preferably a medical solution used to scavenge toxic or allergenic compounds in body fluids.

Method

The invention further relates to a method for stabilising or scavenging the decomposition of carbohydrate components produced in a medical solution during sterilisation and/or storage, comprising providing a sulphite compound to the solution prior or after the sterilisation process in order to reduce decomposition of the carbohydrate components in the medical solution.

Preferably the method is used for preparation of medical solution(s) used for peritoneal dialysis.

Even more preferably the medical solution (s) is/are used in a multiple compartment container for peritoneal dialysis, such as a three compartment container.

Preferably, the method is used for preparation of a multiple compartment container used for peritoneal dialysis, wherein the sulphite compound may be added either to the carbohydrate compartment or to the electrolyte compartment of a multiple compartment.

If a monosulphite compound is used it is preferably added to the carbohydrate solution in an amount to give a concentration in the final solution within the range of 0.01 - 10 mM, preferably 0.05 - 1 mM, most preferably 0.05 - 0.5 mM.

If a disulphite compound is used it is preferably added to the carbohydrate solution in an amount to give a concentration in the final solution within the range of 0.005 - 5 mM, preferably 0.025 - 0.5 mM, most preferably 0.025 - 0.25 mM.

When a disulphite compound is used it is also preferably added in an amount to give a concentration in the final solution which is half of the concentration used for a corresponding monosulphite compound.

The pH of the carbohydrate compartment is preferably between pH 2.0-7.5, more preferably pH 2-5.5, even more preferably pH 3-4 and most preferably about pH 3.2.

More preferably the method is used for the preparation of a sterile multiple compartment.

Additionally, the sulphite compound is provided to the carbohydrate solution prior or after sterilisation.

Furthermore, the sterilisation is performed using any conventional sterilisation method as defined above under the term "sterilisation". Preferably the sterilisation is performed by heat treatment within the range of 100-150° C, for 1-130 minutes, more preferably at 121° C for 20 minutes (Ph. Eur. (current)).

The method according to the invention is intended to be used for medical solutions, in which the medical solution needs to be sterile, by a method as defined under the term "sterilisation", and preferably the method will be used for the preparation of medical solutions used for peritoneal dialysis or the like. By way of adding a sulphite compound in small amounts to the solution either prior or after sterilisation, decomposition of the carbohydrate components into toxic compounds in the solution is prevented or the toxic compounds are scavenged. Preferably, medical solutions to be used for peritoneal dialysis, preferably contain glucose in an amount to give a glucose concentration range between 1.5 to 4%, preferably about 1.5, 2.5 or 4 % by weight in the final solution.

Furthermore the sulphite compound could be used as an antioxidant or to scavenge toxic or allergenic compounds *in vivo*, such as in the body fluids.

Additionally the invention provides the use of a carbohydrate containing solution for the preparation of a multiple compartment container, preferably a three compartment container, suitable for peritoneal dialysis.

Specifically the invention provides the use of a carbohydrate containing solution for the preparation of a multiple compartment container for the treatment of an animal in need thereof.

MATERIALS AND METHODS

Determination of glucose degradation products:

Chemicals: Acetonitrile (Lab Scan, Ireland) and methanol (Lab Scan, Ireland) were of HPLC grade. 2,3- diaminonaphtalene was supplied by ICN, USA. 3-deoxyglucosone 56 % (weight/weight) was synthesised by T. Henle Technische Univerität Dresden. Sodiumphosphate p.a. and Glyoxal 30 % (weight/volume) supplied by Merck (Germany), methylglyoxal 40 % (weight/volume), 2,4-di-

nitrophenylhydrazine (2,4-DNPH) and 1,2-phenylenediamine were supplied by Sigma Chemical (USA). Acetaldehyde p.a. was supplied by Fluka (Germany).

Equipment: Two HPLC systems were used for the determination of glucose degradation products (GDP). One HPLC consisted of an Hewlett Packard liquid chromatograph serie 1050 equipped with an UV-detector and an autosampler. The second HPLC system consisted of an Hewlett Packard liquid chromatograph serie 1100 equipped with an autosampler and Waters Refractive Index detector model 410. Hewlett Packard Chem Station software rev. A.06.03, NT 4.0 was used for the data handling.

Determination of 3-deoxyglucosone *(3-DG):* 3-DG was determined using 2,3-diaminonaphtalene as derivative reagent. The samples were diluted 50 times to a total volume of 1 ml prior to analysis. The standards were prepared in the range 1-6 μM. Standards and samples were prepared by adding 100μl 0.1% (2,3-diaminonaphtalene to 1 ml sample and incubated for 16 hours in room temperature in dark. The analytical column was a Water Symmetry C18 column (5 μm, 25 cm x4, 6 mm). The elution of the substance was performed at constant flow rate of 1.0 ml/min by using a gradient of acetonitrile/water. The percentage of acetonitrile/water (volume/volume) was initially 25/75, and 12 minutes later 25/75, at 15 minutes 60/40 and at the gradient stop 30 minutes 60/40. The wavelength was set at 268 nm and the injected volume was 20 μl. The limit of quantification was 1μM.

Determination of acetaldehyde and formaldehyde: The samples for the determination of acetaldehyde were diluted 20 times to a final volume of 4 ml, prior to analysis. Acetaldehyde was prepared as hydrazone derivatives using 2,4-DNPH as derivative reagent. The standards were prepared in range 1.1 - 11.4 μM acetaldehyde, and 1.7-16.7 μM formaldehyde. Standards and samples were prepared by adding 2 ml 0.08 % (weight/volume) 2,4-DNPH to 4 ml of each sample. The sample were concentrated on a solid phase extraction C18 column (Bond Elut LRC 200 mg/3 ml) and after rinsing with water, eluted with 1.6 ml acetonitrile. The analytical column was a Supelco C18 column (5 μm, 15 cm x 4,6 mm). The elution of the substances was performed at constant flow of 1.7 ml/min by using a linear

gradient of acetonitrile/water. The percentage acetonitrile/water (volume/volume) was initially 35/65 and at the gradient stop 12 minutes later 80/20. The wavelenght was set at 240 nm and the injected volume was 20 μl. The limit of quantification was for acetaldehyde. 1.1 μM. And for formaldehyde 1.7 μM.

Determination of glyoxal and methylglyoxal: Glyoxal and methylglyoxal were determined as quinoxalines using 1,2-phenylenediamine. The standards were prepared in the range 3.5-51.7 μM methylglyoxal. Standards and samples were prepared by adding 0.6 ml 0.4 % (volume/volume) 1,2-phenylenediamine to 1 ml of each sample. The analytical column was Supelco C18 column (5 μm, 25 cm x 4,6 mm). The elution of the substances was performed at constant flow of 1.0 ml / min using a mobile phase of initial 25 % (volume/volume) acetonitrile and 75 % (weight/volume) 0.05 M sodiumphosphate. At the gradient at 6 minutes the mobile phase was 30 % acetonitrile and 70 % millipore water and at gradient stop 9 minutes the percentages were 25/75. The wavelength was set at 312 nm and the injected volume was 20 μl. The limit of quantification for glyoxal was 3.5 μM and for methylglyoxal 2.8 μM.

<u>In vitro assay for cytotoxicity</u>

Medical solutions used for peritoneal dialysis were mixed with one part cell growth medium and 10% (volume/volume) fetal calf serum was added (Wieslander et al., 1991, Kidney Int. 40:77-79). Basal cytotoxicity of medical solution used for peritoneal dialysis were determined on mouse fibroblasts cells L-929 (CCL-1; ATTC, Rockville, MD, USA) as described earlier (Wieslander et al. 1993, Advances in Peritoneal Dialys, 9:31-35) and expressed as inhibition of cellgrowth (ICG).

EXAMPLE 1.

<u>Three compartment container with sulphite in the glucose compartment</u>

A multiple compartment container as shown in FIG. 1, containing following medical solutions in the three compartments 44, 45 and 9.

<u>Compartment 44 containing 100 ml of the composition:</u>

glucose	30%
calcium	20 mM
magnesium	5 mM
sodium	132 mM
bisulphite	1 mM
pH 3.2	

<u>Compartment 45 contains 100 ml of the composition:</u>

glucose	50%
calcium	33 mM
magnesium	8 mM
sodium	132 mM
bisulphite	1 mM
pH 3.2	

<u>Compartment 9 contains 1900 ml with the composition:</u>

bicarbonate	40 mM
sodium	132 mM
pH 6.7	

By mixing the contents of compartment 44 and compartment 9, a final solution suited for peritoneal dialysis is obtained with the following concentrations:

glucose	1.5%
calcium	1.0 mM
bicarbonate	38 mM
sodium	132 mM

magnesium	0.25 mM
bisulphite	0.05 mM

By mixing the contents of compartment 45 and compartment 9, a final solution suited for peritoneal dialysis is obtained with the following concentrations:

glucose	2.5%
calcium	1.65 mM
bicarbonate	38 mM
sodium	132 mM
magnesium	0.4 mM
bisulphite	0.05 mM

By mixing the contents of both compartments 44 and 45 with the contents of compartment 9, a final solution suited for peritoneal dialysis is obtained with the following concentrations:

glucose	4.0%
calcium	2.5 mM
bicarbonate	36 mM
sodium	132 mM
magnesium	0.6 mM
bisulphite	0.1 mM

EXAMPLE 2.

Three compartment container with sulphite in electrolyte compartment

A multiple compartment container as shown in FIG. 1, containing following medical solutions in the three compartments 44, 45 and 9.

<u>Compartment 44 contains 100 ml of the composition:</u>

glucose	30%
calcium	20 mM
magnesium	5 mM
sodium	132 mM
pH 3.2	

<u>Compartment 45 contains 100 ml of the composition:</u>

glucose	50%
calcium	33 mM
magnesium	8 mM
sodium	132 mM
pH 3.2	

<u>Compartment 9 contains 1900 ml with the composition:</u>

bicarbonate	40 mM
sodium	132 mM
bisulphite	0.1 mM
pH 6.7	

By mixing the contents of compartment 44 and compartment 9, a final solution suited for peritoneal dialysis is obtained with the following concentration:

glucose	1.5%
calcium	1.0 mM
bicarbonate	38 mM
sodium	132 mM
magnesium	0.25 mM
bisulphite	0.095 mM

By mixing the contents of compartment 45 and compartment 9, a final solution suite for peritoneal dialysis is obtained with the following concentration:

glucose	2.5%
calcium	1.65 mM
bicarbonate	38 mM
sodium	132 mM
magnesium	0.4 mM
bisulphite	0.095 mM

By mixing the contents of both compartments 44 and 45 with the contents of compartment 9, a final solution suited for peritoneal dialysis is obtained with the following concentration:

glucose	4.0%
calcium	2.5 mM
bicarbonate	36 mM
sodium	132 mM
magnesium	0.6 mM
bisulphite	0.090 mM

EXAMPLE 3

<u>Two compartment container with sulphite in glucose compartment or three compartment container with both glucose compartments mixed.</u>

The solutions used in example 3 and 4 were as described in example 1 and 2 except for that 50 % glucose was used in all glucose compartments giving slightly different volumes for the compartments.

Two different sets of solutions were prepared, one electrolyte compartment with the volume 1.875 L and one glucose containing compartment with different amounts of bisulphite added, this volume was 125 ml. The solutions were sterilised at 121° C for 1 hour and mixed post sterilisation. The concentrations post mixing of

electrolytes were 132 mM Na^+, 1.35 mM Ca^+, 0.25 mM Mg^{2+}, 95.2 mM Cl^- and 40 mM lactate.

The concentration of glucose were 4 % (w/v) and the concentration of sulphite were 0. 0.01, 0.05, 0.1, 0.2 and 0.5 mM in the final solution.

The sterilised solutions were analysed in the *In vitro assay of cytotoxicity* mentioned under Materials & Methods. The results from the assay showed that an increase of the sodium bisulphite resulted in a decrease of the ICG value, which means that there is a decrease in the content of the toxic decomposition products after addition of a sodium bisulphite.

EXAMPLE 4

Two compartment container with sulphite in electrolyte compartment or three compartment container with both glucose compartments mixed

As described in example 3 except for that sulphite was added to the electrolyte compartment. The concentrations of electrolytes, glucose and sulphite in the final solution were as in example 3. The sterilised solutions were analysed as in example 3. The results from the assay showed that an increase of the sodium bisulphite resulted in a decrease of the ICG value, which means that there is a decrease in the content of the toxic decomposition products.

EXAMPLE 5

Analysis of a solution with or without sulphite for the presence of formaldehyde acetaldehyde and ICG.

Three solutions containing 132 mM Na^+, 1.35 mM Ca^{2+}, 0.25 mM Mg^{2+}, 95.2 mM Cl^-, 40 mM lactate and 1.5 % glucose was heat sterilised at 121° C for 1 hour. The sterilised solutions were mixed with sodium bisulphite to three different concentrations of sodium bisulphite (0, 0.5, 1 mM).

Three solutions containing 132 mM Na^+, 1.35 mM Ca^{2+}, 0.25 mM Mg^{2+}, 95.2 mM Cl^-, 40 mM lactate and 1.5 % glucose were mixed with sodium bisulfite to different

concentration of sodium bisulphite (0, 0.5, 1 mM) and was heat sterilised at 121° C for 1 hour.

The sterilised six solutions were analysed in the *In vitro assay of cytotoxicity* and *determination of acetaldehyde and formaldehyde* mentioned under Materials & Methods. The results from the *In vitro assay of cytotoxicity* showed that an increase of the sodium bisulphite resulted in a decrease of the ICG value, which means that there is a decrease in the content of the toxic decomposition products. The results from the assay " *determination of acetaldehyde and formaldehyde*" showed decreased levels of both acetaldehyde and formaldehyde in the solutions containing sodium bisulphite, even down to levels under detection limit.

CLAIMS

1. Multiple compartment container for sterile medical solutions, wherein said solutions are present in two or more compartments, and at least one of said solutions comprises a carbohydrate compound, **characterised** in that at least one sulphite compound is present in one or more of said compartments.

2. Multiple compartment container according to claim 1, **wherein** said sulphite compound is selected from the group consisting of HSO_3^-, $S_2O_5^{2-}$ or SO_3^{2-}, having a positive counter ion or mixtures thereof, preferably $NaHSO_3$, $Na_2S_2O_5$ or Na_2SO_3 or a mixture thereof.

3. Multiple compartment container according claim 1 or 2, **wherein** said sulphite compound is a monosulphite compound, the total amount of monosulphite compound in said container being equal to 0.01-10 mmol, per liter of the total amount of solution in said container, preferably 0.05 - 1 mmol, per liter of the total amount of solution in said container, most preferably 0.05 - 0.5 mmol, per liter of the total amount of solution in said container.

4. Multiple compartment container according to claim 1 or 2, **wherein** said sulphite compound is a disulphite compound, the total amount of disulphite compound in said container being equal to 0.005-5 mmol per liter of the total amount of solution in said container, preferably 0.025 - 0.5 mmol, per liter of the total amount of solution in said container, most preferably 0.025 - 0.25 mmol, per liter of the total amount of solution in said container.

5. Multiple compartment container according to claim 3 or 4, **wherein** the pH of the mixed solution in said container is between 5.0 – 8.0, more preferably between 6.0 – 8.0, most preferably between 7.0 – 7.5.

6. Multiple compartment container according to any of claims 1-5, **wherein** said carbohydrate is glucose and the total amount of glucose in said container is about 4% by weight of the total amount of solution in said container.

7. Multiple compartment container according claims 1 to 6, **wherein** said carbohydrate compound is not present in all compartments, preferably in only one of

two compartments in a two compartment bag or in only two of three compartments in a three compartment bag.

8. Multiple compartment container according claim 7, **wherein** the pH of said compartments containing said carbohydrate compound is between 2.0 and 7,5, preferably between 2.0 and 5,5, more preferably between 3 and 4 and most preferably about 3,2.

9. Multiple compartment container according to claim 7 or 8, **wherein** said sulphite is a monosulphite compound and wherein said concentration monosulphite after mixing of said different solutions give rise to a final solution with a concentration of monosulphite compound of 0.01-10 mM, preferably 0.05 - 1 mM, most preferably 0.025 - 0.25 mM.

10. Multiple compartment container according to claim 7 or 8, **wherein** said sulphite is a disulphite compound and wherein said concentration disulphite after mixing of said different solutions give rise to a final solution with a concentration of disulphite compound of 0.005-5 mM, preferably 0.025 - 0.5 mM, most preferably 0.025 - 0.25 mM.

11. Multiple compartment container according to any of claims 7 to 10, **wherein** said carbohydrate compound is glucose and said container is a three compartment bag and wherein the concentration of glucose after mixing of said different solutions give rise to a final solution in the range of 1.5 to 4%, preferably about 1.5, 2.5 or 4% by weight of glucose based of the total amount of final solution.

12. Multiple compartment container according to any of claims 1-11, **wherein** said container is sterilised using heat treatment.

13.Multiple compartment container according to any of claims 1-12, **wherein** said multiple compartment container contains medical solutions for preparing a final solution for peritoneal dialyses by mixing two or more of said medical solutions.

14. A sterile medical solution comprising a carbohydrate compound, at least one sulphite compound selected from the group consisting of HSO_3^-, $S_2O_5^{2-}$ or SO_3^{2-}, having a positive counter ion or mixtures thereof, preferably $NaHSO_3$, $Na_2S_2O_5$ or

Na_2SO_3 or a mixture thereof, wherein said sulphite compound is a monosulphite compound, present in a concentration of between 0.01-10 mM or a disulphite compound, present in a concentration of between 0.005-5 mM.

15. A sterile medical solution according to claim 14, wherein said sulphite compound is a monosulphite compound, present in a concentration of preferably 0.05 - 1 mM, most preferably 0.05 - 0.5 mM.

16. A sterile medical solution according to claim 14 or 15, wherein said solution is heat sterilised.

17. A sterile medical solution according to any of claims 14-16, wherein said solution is a solution for peritoneal dialysis.

18. A sterile medical solution according to any of claims 14-17, wherein said solution is used in a three compartment container.

19. A method of stabilising a carbohydrate containing sterile medical solution wherein in that at least one sulphite compound is added to said solution in a concentration of preferably 0.05 - 1 mM, most preferably 0.05 - 0.5 mM if said sulphite component is a monosulphite compound, and in a concentration of 0.005-5 mM, preferably 0.025 - 0.5 mM, most preferably 0.025 - 0.25 mM if said sulphite component is a disulphite compound.

20. A method according to claim 19, wherein said sulphite compound is selected from the group consisting of HSO_3^-, $S_2O_5^{2-}$ or SO_3^{2-}, having a positive counter ion or mixtures thereof, preferably $NaHSO_3$, $Na_2S_2O_5$ or Na_2SO_3 or a mixture thereof.

21. A method according to claim 19 or 20, wherein said solution is heat sterilised.

22. Use of a carbohydrate containing sterile medical solution according to any of claims 14-18 for the preparation of a multiple compartment container according to any of claims 1-13.

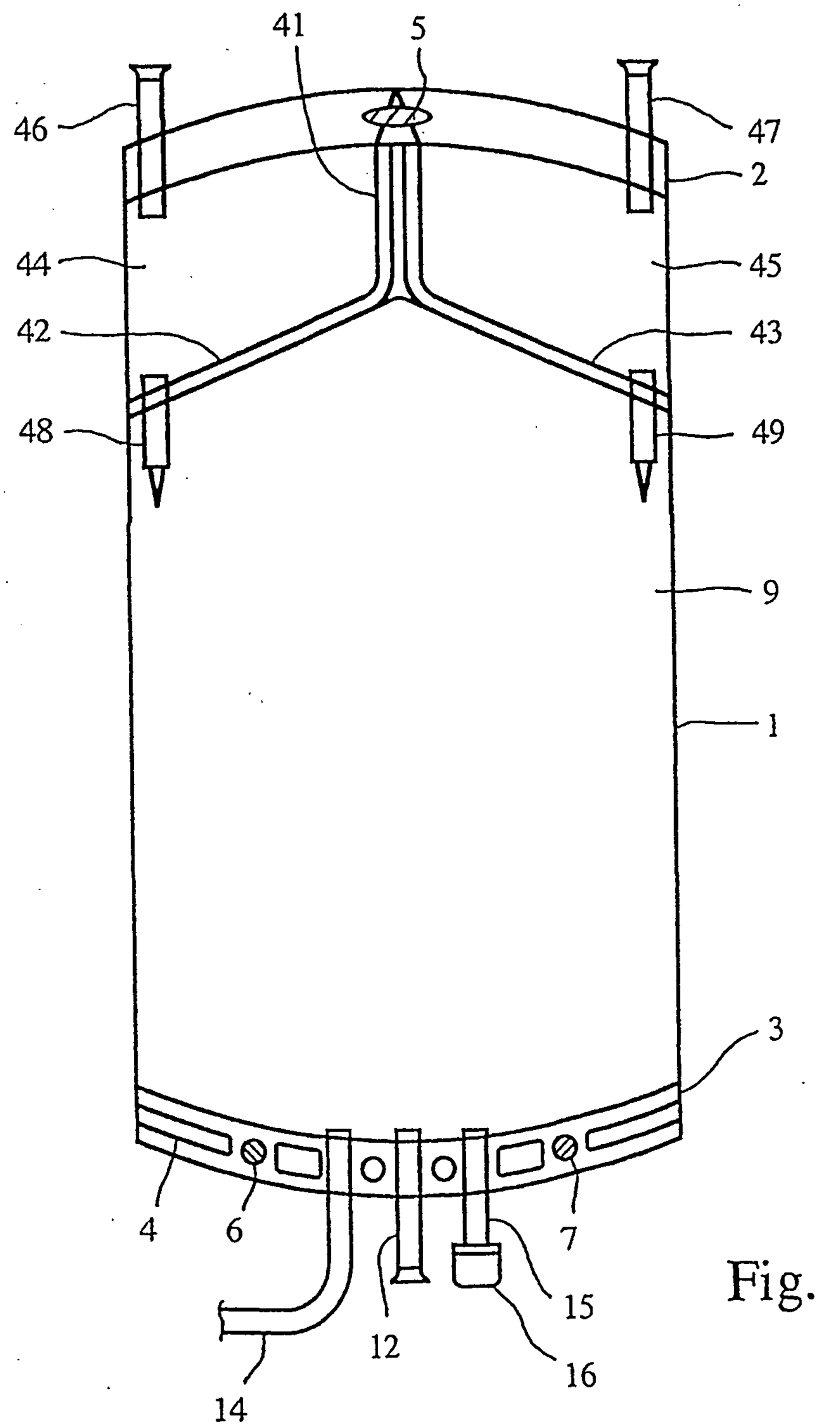

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01125

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/08, A61K 31/70, A61K 31/10, A61M 1/28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4339433 A (KARTINOS ET AL), 13 July 1982 (13.07.82), column 2, line 63; column 4, line 25; column 11, line 55 --	1-22
X	Cancer Research, Volume 43, March 1983, Stephen B. Howell et al, "Intraperitoneal cis-Diamminedichloroplatinum with Systemic Thiosulfate Protection", page 1426 - page 1431, page 1426, table 2 --	14-22
X	Journal of Pharmaceutical Sciences, Volume 54, 1965, Sami F. Halaby et al, "Absorption of Sodium Bisulfite from Peritoneal Dialysis Solutions" page 52 - page 55; page 52 --	14-22

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 Sept 2001	21 -09- 2001

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Toxicology, Volume 30, No 4, 1992, Susan C. Smolinske, B.S., "Review of parenteral sulfite reactions", page 597 - page 606, conclusion --	1-22
X	Z. Ernährungswiss., Volume 18, 1979, K. Lang et al, "Sulfit in Infusionslösungen" page 37 - page 41 --	1-22
Y	WO 9519778 A1 (BAXTER INTERNATIONAL INC.), 27 July 1995 (27.07.95) --	1-22
Y	WO 9705852 A1 (GAMBRO AB), 20 February 1997 (20.02.97) --	1-22
A	Peritoneal Dialysis International, Volume 15, No 7, 1995, Anders P. Wieslander et al, "Heat sterilization of glucose-containing fluids for peritoneal dialysis: Biological consequences of chemical alterations" page 52 - page 60 -- --------	1-22

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Information on patent family members

03/09/01

International application No.
PCT/SE 01/01125

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